

# Corpus callosum morphology of Williams syndrome: relation to genetics and behavior

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As the largest interhemispheric commissure in the brain, the corpus callosum is of particular interest in disorders that may preferentially affect white matter development such as Williams syndrome (WS). Individuals with WS possess a remarkable array of neurobehavioral peaks and valleys, including deficits in visuospatial ability, mathematics, and attention, but with relative preservation of language and affect. Our study measured the corpus callosum and its primary subdivisions using high-resolution MRI in 20 individuals with WS (13 females and seven males; mean age 28.5, SD 8.3 years; range 19 to 44 years) and 20 age- and sex-matched control participants (mean age 28.5, SD 8.2 years; range 19 to 48 years). Total midsagittal corpus callosum area was reduced ( $F=4.5$ ,  $p=0.04$ ,  $df=36$ ) in the WS population. The area of the splenium ( $F=12.4$ ,  $p=0.001$ ,  $df=36$ ) and isthmus ( $F=9.4$ ,  $p=0.004$ ,  $df=36$ ) were disproportionately reduced in WS beyond the absolute reduction of the entire corpus callosum. These reductions are in concordance with other neuroanatomical findings of decreased parietooccipital volumes as well as the observed visuospatial problems associated with WS.

Genetic syndromes possessing relatively consistent behavioral phenotypes provide rare opportunities to examine the relations between genetics, neuroanatomy, and neurobehavior. Specifically, Williams syndrome (WS), a condition characterized by the spontaneous hemizygous deletion of approximately 25 genes in the 7q11.23 region of the genome, is associated with an unusual array of cognitive symptoms (Ewart et al. 1993; Brondum-Nielsen et al. 1997; Korenberg et al. 1997, 2000). These symptoms include severe deficits in visuospatial ability and problem solving, but with relative strength of language abilities, and facial processing at the level of normally developing individuals (Bellugi et al. 1990, 1996, 2000; Wang and Bellugi 1994; Wang et al. 1995). Individuals with WS also display several characteristic behavioral features such as attention deficit, hypersociality, and a marked fascination with music (Bellugi et al. 1990, Bawden et al. 1997, Levitin and Bellugi 1998). This unique neurocognitive profile of WS in conjunction with its known genetic etiology provides investigators with the chance to explore links between genes and cognitive functions.

Neuroanatomical investigations of the WS brain have revealed a distinct morphology when compared both to normally developing individuals and to those with other genetic disorders. Individuals with WS have brain volumes significantly reduced when compared to normally developing individuals (Jernigan and Bellugi 1990, Jernigan et al. 1993). However, volume decreases are not uniform throughout the brain. While individuals with WS demonstrate particularly robust reductions in the volume of parietal and occipital regions, the frontal and temporal lobes, amygdala, hippocampus, parahippocampal gyrus, and the cerebellum are relatively spared or even larger than in normally developing individuals (Jernigan et al. 1993, Reiss et al. 2000). In addition, our laboratories have detected significant white matter volume reductions in the WS brain, particularly in the posterior half of the cerebrum (Reiss et al. 2000).

Due to the fact that the WS deletion appears to affect white matter more than gray, the morphology of the corpus callosum (CC) is of great interest. The CC is critical to the higher cognitive processes of bilateral sensory integration, language, and visuospatial processing (Shanks et al. 1975, DeLacoste-Utamsing and Holloway 1982, Hines et al. 1992, Giedd et al. 1996), which are all unusual in WS (Bellugi et al. 1999). This study investigates how the size of the CC and its subdivisions in WS differ from that of normally developing individuals and the potential relation of these differences to cognitive function.

## Method

### PARTICIPANTS

Twenty participants diagnosed with WS (13 females and seven males; mean age 28.5, SD 8.3 years; range 19 to 44 years) and 20 normally developing control participants individually matched for age and sex (mean age 28.5, SD 8.2 years; range 19 to 48 years) were recruited by the Laboratory for Cognitive Neuroscience at the Salk Institute, CA, USA. The diagnoses of WS were made by a medical geneticist or other physician familiar with WS. In addition, WS was confirmed genetically by fluorescent in situ hybridization probes for elastin: a gene consistently found in the critical deletion region associated with WS (Giedd et al. 1996, Korenberg et al. 1997). All diagnoses were further confirmed using the

Williams Syndrome Association's diagnostic score sheet (Williams Medical Questionnaire, The Salk Institute for Biological Studies).

Each individual gave informed consent for their participation in the study via consent forms that were approved by the internal review board at the Salk Institute. Some of those with WS in this study have been in other neuroimaging studies previously reported by our research group (Reiss et al. 2000).

**IMAGING**

MRI of each participant's brain was acquired using a 1.5 T GE-Signa Scanner (General Electric, Milwaukee, WI, USA). The images were acquired in the sagittal plane with a volumetric 3D-radio frequency spoiled gradient echo protocol (TR=24, TE=5, flip angle=45 NEX=2 matrix size=256x192, field of view=24 cm, slice thickness=1.2 mm). Thirty-eight of

the scans were acquired at the University of California, San Diego Medical Center. The remaining two scans, both control participants, were acquired using an identical scanner and pulse sequence at Stanford University Medical Center.

All scans were imported into the program BrainImage 3.X (Reiss 2000) for blinded image processing and analysis. Measurement of the CC was based on a previously existing protocol (Baumgardner et al. 1996). This protocol consists of: (1) determining the best midsagittal slice (derived by rotating the brain in three dimensions) based on clarity of the CC, cerebellar vermis, cerebral aqueduct, and spinal cord; (2) manually circumscribing the CC; and (3) measuring the area of the CC and its subdivisions automatically using algorithms built in to BrainImage. Interrater reliability for CC measurement as determined by the intraclass correlation coefficient for 10 datasets was 0.89.

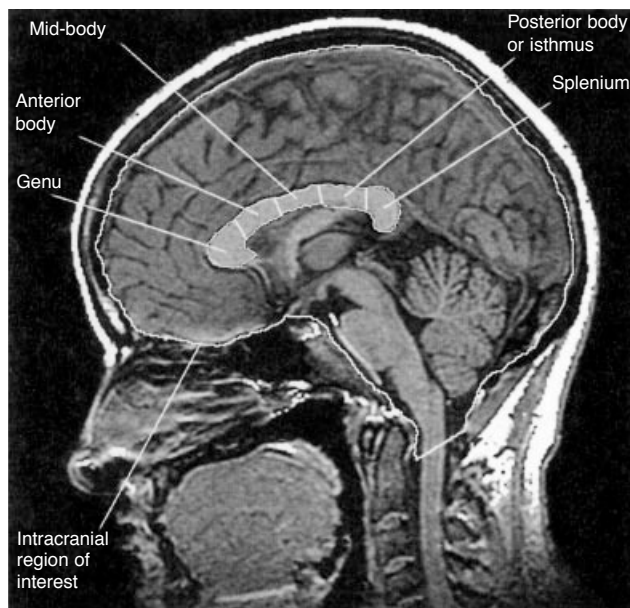
To determine the boundaries of the CC subdivisions, the CC centerline was first determined using BrainImage's medial axis transform algorithm (Allen et al. 1991, Peterson et al. 1993). Subdivisions of the CC were then defined by four equidistant lines automatically drawn orthogonal to the centerline, dividing the CC into five segments, as shown in Figure 1.

Due to the fact that brain size can have a large effect on the size of the WS, a region of interest encompassing the intracranial space was drawn and measured for each participant to use as a covariate in the analyses. The intracranial area was circumscribed by following the interior of the cranial bone (following the marrow of the basiocciput), including optic chiasma and the pituitary stalk, but excluding the sella turcica (Scnitzlein 1985). The inferior border was defined by a line drawn between the tip of the foramen magnum to the dens. Interrater reliability for this variable as determined from 10 datasets was 0.98.

**Table I: Summary of corpus callosum area findings (cm<sup>2</sup>)**

Region	WS mean (SD)	Control mean (SD)	ANCOVA <sup>a</sup> p
Corpus callosum	6.81 (0.95)	7.82 (0.73)	0.04
Genu	1.50 (0.26)	1.72 (0.21)	ns
Rostrum	1.33 (0.25)	1.41 (0.16)	ns
Mid-body	1.21 (0.21)	1.35 (0.13)	ns
Isthmus	1.04 (0.20)	1.27 (0.17)	0.004
Splenium	1.74 (0.26)	2.10 (0.20)	0.007

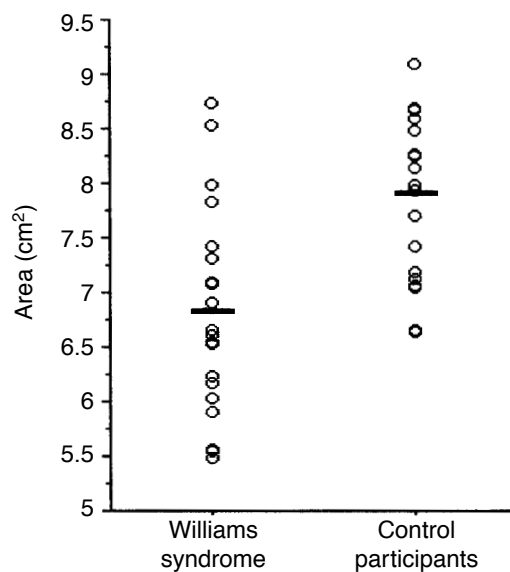
<sup>a</sup>ANCOVA between groups for each structure were covaried for age and intracranial area.



**Figure 1: Summary of regions of interest studied (highlighted in white). Circumscription of intracranial area followed cranial bone. Inferior border of intracranium was formed by drawing a line from foramen magnum to dens. Only outer border of corpus callosum was drawn by hand; subdivisions were created by an automated algorithm.**

**DATA ANALYSIS**

All data were first inspected for normality to insure that the use of parametric statistics was warranted. Analyses of



**Figure 2: Area of corpus callosum divided by group. Black lines represent mean values for each group.**

covariance (ANCOVA) were then performed. To account for the effects of age and brain size on CC area, both age and intracranial area were used as covariates for all analyses unless otherwise specified. A two-sided  $p$  value of  $<0.05$  was used as the significance level. A priori hypotheses were based on previous volumetric data generated by our laboratory (Reiss et al. 2000). These hypotheses included: (1) that the size of the CC would be reduced in participants with WS compared to normally developing participants, and (2) reductions in CC size would be particular concentrated in posterior brain regions where lobar reductions had previously been demonstrated.

### Results

Table 1 summarizes the data described below. As shown in Figure 2, the mean total area of the CC was reduced in those with WS when compared to the control group (ANCOVA  $F=4.5$ ,  $p=0.04$ ,  $df=36$ ). In addition, significant reductions in the area of the splenium (ANCOVA:  $F=12.4$ ,  $p=0.001$ ,  $df=36$ ) and isthmus (ANCOVA  $F=9.4$ ,  $p=0.004$ ,  $df=36$ ) in the WS population were detected (Fig. 3).

The average area of the genu was reduced in WS. Though in absolute terms this reduction is significant (ANOVA  $F=8.3$ ,  $p=0.007$ ,  $df=38$ ), it is not significant after covarying for age and the proportionally smaller size of the WS brain (ANCOVA  $F=1.4$ ,  $p=0.24$ ,  $df=36$ ). In WS, the mid-body of the CC also was significantly smaller in the WS group (ANOVA  $F=6.0$ ,  $p=0.02$ ,  $df=38$ ); however, significant findings were no longer observed after covarying for age and intracranial area (ANCOVA  $F=1.9$ ,  $p=0.18$ ,  $df=36$ ). The anterior body of the CC in WS was not found to be significantly different from the control group (ANOVA  $F=1.5$ ,  $p=0.22$ ,  $df=38$ ).

### Discussion

The posterior regions of the CC (isthmus and splenium) were found to be significantly reduced in WS relative to the control group. Interestingly, the isthmus and the splenium contain the vast majority of white matter tracts that bilaterally

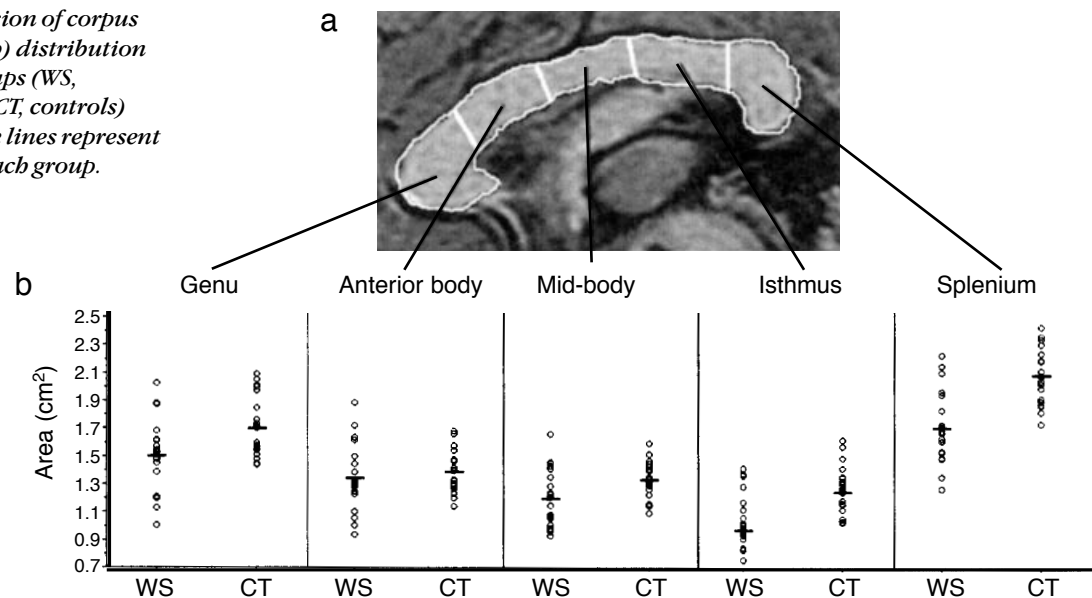
connect the visual and visual association areas of the brain (de Lacoste et al. 1985). Thus the neuroanatomical findings reported here appear to concur with the well-known visual-spatial difficulties ascribed to WS and suggest a possible neuroanatomical correlate (Wang et al. 1995, Bellugi et al. 1999). The overall shape of the CC in WS follows the general morphological trends previously observed in this condition: relatively preserved anterior regions with decreases in size posteriorly.

The relative preservation of the genu, mid-body, and rostrum concurs with neuroanatomical volumetric findings showing that the frontal and temporal lobes, which are connected via the anterior three-fifths of the CC, also are relatively preserved in WS (de Lacoste et al. 1985, Jernigan et al. 1993, Reiss et al. 2000). This finding agrees with the known neurobehavioral profile of WS, in which relative preservation of frontal- and temporal-lobe functions such as language and affect are observed in affected individuals (Bellugi et al. 1999).

Dysgenesis of the CC has been reported in several other groups with mental retardation\* and appears to be a relatively common trait in several neurogenetic, psychiatric, and neurological disorders (Bodensteiner et al. 1994, Gabrielli et al. 1998). As in WS, studies in other neurodevelopmental disorders typically have shown an overall decrease in the size of the CC, though some studies have shown significant increases as well (Baumgardner et al. 1996, Kivitie-Kallio et al. 1998). The few studies that have subdivided the CC show that specific regions are disproportionately affected in several conditions (Wang et al. 1992, Swayze et al. 1997, Manes et al. 1999). However, there does not appear to be a typical pattern of CC reduction that is characteristic of non-specific mental retardation; the extant studies show variation in targeted CC deficits between neurodevelopmental groups. In general, localized reductions in the size of CC subregions have been shown to be diagnostic of global brain reductions, with regional CC size correlated with the volumes of related cortical regions

\*US usage. UK usage: learning disability.

**Figure 3:** (a) Subdivision of corpus callosum, showing (b) distribution of areas for both groups (WS, Williams syndrome; CT, controls) and subregion. Black lines represent the mean value for each group.



(Barkovich and Norman 1988).

The only other MRI study examining callosal morphology in WS (Wang et al. 1992) found a similar preservation of the rostral CC when compared to normally developing individuals, while a group with Down syndrome demonstrated reductions in this area (Wang et al. 1992). However, unlike in the present study, no disproportionate reductions in the posterior regions of the CC in WS were reported, though the overall CC size was significantly decreased. This discrepancy may be owed to the larger sample size used here (20 participants with WS versus 11 participants in the Wang et al. study) or perhaps to the thinner MRI slices (1.2 versus 5 mm slices) in our study. In addition, the Wang et al. study was limited to selecting the best mid-sagittal slice from the acquired MRI images; newer technology used in the present study could treat the brain as a three-dimensional object, enabling precise determination of the best plane through the CC.

Significant differences in the callosal size of those with WS strengthen arguments that one or more genes in the critical WS deletion region are involved in neurodevelopment. Histological studies by Galaburda and colleagues have shown an increase in cellular density and a decrease in the cellular organization of cortical neurons, as well as incomplete axonal myelination in WS (Galaburda et al. 1994). These features suggest an arrest early in postnatal development (Conel 1967, Galaburda et al. 1994). Of particular interest to the present study is the evidence that neurons in cortical regions tend to orient themselves improperly in WS, which could be caused by abnormal afferent pathways from the CC (Galaburda et al. 1994). The decreased size of the CC also could be related to the abnormalities in myelination observed in WS, though the posterior specificity of the CC reduction suggests that the effect of the genetic deletion is more targeted.

Several genes in the WS deletion region are members of gene-families that play well-known developmental roles. In particular, LIM-kinase1 has been shown to play a role in growth cone formation and axon guidance, which may partially underlie abnormal brain development in WS (Arber et al. 1998, Yang et al. 1998). Indeed, LIM-kinase1 has been correlated with visuospatial deficits in WS (Frangiskakis et al. 1996, Monaco 1996, Tassabehji et al. 1996, Carraway et al. 1997). This finding, in conjunction with its known role in axon guidance, makes hemizyosity for LIM-kinase1 a possible contributor to reductions in callosal size associated with WS. More research is required in this field, particularly on those with WS who have partial deletions, in order to dissociate the many intriguing genetic, neuroanatomic, behavioral, and neurocognitive components of this syndrome. Investigations using diffusion tensor imaging in particular, which allows visualization of white matter directionality, could provide valuable clues as to how brain connectivity of WS differs from other groups.

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